



Case series

Pilot study assessing ^{18}F -fluorothymidine PET/CT in cervical and vaginal cancers before and after external beam radiation[☆]

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ABSTRACT

Objective: The role of F-18-fluorothymidine (FLT) PET-CT imaging in the evaluation of gynecologic cancers has not been established. We sought to evaluate (FLT) PET-CT imaging in gynecologic cancers by comparing standard uptake values (SUVs) of FLT with F-18-fluorodeoxyglucose (FDG) PET in the primary tumor at diagnosis, and assess FLT uptake immediately following concurrent chemoradiotherapy (chemoRT).

Methods: In this pilot study, patients treated for cervical (5) or vaginal (1) cancer underwent FLT-PET and FDG-PET scanning at diagnosis (FLT1 and FDG1). Five patients (4 cervical and 1 vaginal) also underwent FLT-PET within 1–3 weeks after chemoRT before brachytherapy (FLT2). Wilcoxon rank-sum test was used to compare the FLT1 and FDG1 parameters.

Results: Median age at diagnosis was 61-years (range, 33–72). Cervical cancers were staged as IB2 (n = 1, 20%), IIB (n = 1, 20%), IIIB (n = 1, 20%) and IVA (n = 2, 40%) and the single vaginal cancer was staged IIIB. The most common histology was squamous cell carcinoma (n = 3, 50%) followed by adenocarcinoma (n = 2, 33%) and clear-cell adenosquamous carcinoma (n = 1, 17%). Median tumor SUV_{max} at diagnosis was 7.8 on FLT1-PET (3.9–14.2) versus 11.6 (5.9–23.2) on FDG1-PET (p = 0.15). Tumor SUV_{max} of FLT declined 54%–100% after chemoRT.

Conclusion: The tumor SUV of FLT at diagnosis was lower than that of FDG-PET. FLT uptake was markedly decreased after chemoRT. Results indicate that there may not be a significant effect of inflammation on FLT uptake in gynecologic cancers. FLT may be a useful tool when assessing the effects of chemoRT on gynecologic malignancies and planning for postchemoRT brachytherapy treatments.

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1. Introduction

Gynecologic malignancies, including cervical and vaginal cancers, often require a multidisciplinary approach that combines radiation, chemotherapy and/or surgery. Imaging modalities that can accurately assess the extent of the disease and the effect of treatments have become an integral component in evaluating the success of therapy.

Radiation therapy is an essential component in the management of unresectable locally advanced disease. More specifically, external beam radiation therapy (EBRT) and brachytherapy (BT) are the two radiation modalities that are used sequentially to reduce the risk of

local recurrence and improve survival. At diagnosis, positron emission tomography/computed tomography (PET/CT) with the tracer 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG) is typically used to detect disease extent. However, studies have indicated that, when FDG-PET is used immediately after EBRT to assess treatment response, it may be difficult to differentiate between residual or recurrent active tumor and inflammation in the area treated with radiation using this tracer (Choi et al., 2014). Therefore, FDG-PET is not a reliable assessment tool to monitor residual tumor and to direct BT doses immediately after EBRT.

Another available PET tracer used for tumor assessment, F-18-fluorothymidine (FLT), has the potential to improve detection of metabolically active tumors (Wang et al., 2015; Hoshikawa et al., 2015). This relatively new radiotracer has attracted attention for evaluation of post-radiation response in, head/neck, esophageal, breast, lung, and rectal cancers though its role in the evaluation of gynecologic cancers after EBRT is unknown (Yue et al., 2010; Lubberink et al., 2012; Wieder et al., 2007; Kahraman et al., 2011; Menda et al., 2009). The fact that

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only proliferating cells (i.e. malignant tissues) enable thymidine incorporation in DNA synthesis makes FLT imaging a particularly attractive tool when differentiating between residual/recurrent malignancy and inflammation (Rasey et al., 2002; Toyohara et al., 2002). The goals of this study were to compare metabolic parameter standard uptake values (SUVs) of FLT with FDG PET in patients with gynecologic cancer at diagnosis and to determine if FLT SUVs are affected by inflammation immediately following EBRT.

2. Material and methods

2.1. Patients

Between August 2012 and April 2014, six patients with newly diagnosed gynecologic cancers treated with concurrent chemoradiotherapy (chemoRT) were enrolled on a prospective clinical trial for image-guided brachytherapy. All tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system (Pecorelli, 2009). The eligibility requirements included: histopathologically confirmed primary lesions (five were cervical cancers and one was vaginal cancer); MRI and/or PET-CT scan within 4 months before registration; age ≥ 18 ; ECOG performance status ≤ 2 ; and no uncontrolled illness that would limit compliance with study requirements. The study was approved by the institutional review board, and all participants signed an informed consent form. The clinicaltrials.gov identification number for this trial is NCT01399658.

2.2. FLT synthesis

The BWH Cyclotron and Radiopharmacy produced FLT in a nucleophilic synthesis box using in-process controls such as high-purity solvents to synthesize the radiopharmaceutical and automated software that controls the temperature and timing parameters and records the information from the production run. An integrity test was performed on the sterilizing filter in addition to a sterility test on the final drug product; the process achieved a radiochemical purity of more than 95%.

2.3. PET/CT acquisition

For both FDG and FLT imaging, PET/CT was performed after at least 4 h of fasting and 60 ± 10 min after the intravenous administration of 370–480 megabecquerels of FDG or 296–370 megabecquerels of FLT. PET imaging was performed in 3-dimensional mode on a Discovery ST PET/CT scanner (General Electric, Milwaukee, WI) from the skull base through the mid thighs. Non-contrast helical CT imaging was performed over the same range without breath-hold for attenuation correction of PET images and anatomic correlation. The review of FDG- and FLT-PET/CT images and measurements of the tumor SUV_{max} were performed on Hermes workstation (Hermes Medical Solutions AB, Stockholm, Sweden).

2.4. Statistical analysis

The Wilcoxon rank sum test was used to compare the SUVs of FLT and FDG at diagnosis. P values of less than 0.05 were considered significant.

3. Results

3.1. Patient and tumor characteristics

The median age at diagnosis for the six patients was 61 years (range, 33–72). The five cervical cancers were staged as IB2 (n = 1, 20%), IIB (n = 1, 20%), IIIB (n = 1, 20%) and IVA (n = 2, 40%) and the one vaginal cancer was stage IIB (n = 1). The most common histology was squamous cell carcinoma (n = 3, 50%) followed by adenocarcinoma

Table 1

Patient summary.

Patient	Age (yrs)	Stage	Primary	Histology	Chemotherapy regimen/cycles	EBRT dose (Gy)
A	72.0	IIIB	Vagina	SCC	CDDP/5	4500
B	33.0	IB2	Cervix	CC	CDDP/5	4500
C	72.0	IIB	Cervix	SCC	CDDP/5	4500
D	49.0	IIIB	Cervix	ACC	CDDP/5	4500
E	59.0	IVA	Cervix	ACC	CDDP/4	4500
F	64.0	IVA	Cervix	SCC	CPT/3	4500

EBRT = external beam radiotherapy, Gy = gray, SCC = squamous cell carcinoma, CC = clear-cell carcinoma, ACC = adenocarcinoma; CDDP = cisplatin, CPT = carboplatin.

(n = 2, 33%) and clear cell adenosquamous carcinoma (n = 1, 17%). Median follow-up time was 24 months (range, 6–30 months).

All six patients received concurrent weekly chemotherapy (cisplatin for 5 and carboplatin for 1) with radiation therapy (Table 1). All received a total radiation dose of 45 Gy in 25 fractions of 1.8 Gy to the pelvis and para-aortic nodes. Patient A received an additional 6 Gy boost to the right inguinal nodes, and patient B received an additional 10 Gy boost to the right iliac nodes.

All patients underwent FLT-PET and FDG-PET scanning at diagnosis; these scans were performed 1–3 weeks before chemoRT. All patients also had post-chemoRT FLT-PET/CT scans before receiving brachytherapy, except patient C due to scanner malfunction (Table 2). All patients had post-chemoRT FDG-PET, but are not reported due to diffuse uptake. At last follow-up, five patients were alive and one had died with the most recent MRI exam showing significant tumor shrinkage 3-months prior to death but the cause was undeterminable. Two patients with primary cervical cancer were known to have had recurrence: 1 in the vaginal cuff (Patient C) and 1 with metastatic disease to the lung (Patient D).

3.2. Comparison of FLT and FDG uptake at diagnosis

At diagnosis, FDG uptake was visually more vivid in the primary tumor in all patients than FLT uptake (Fig. 1). The median SUV_{max} at diagnosis was 6.9 (range, 3.9–14.2) for FLT-PET and 11.6 (range, 5.9–23.2) for FDG-PET. SUVs were 1.5–3.5 times higher for FDG than for FLT in 4 patients; the other two patients only had minor differences between the SUVs of the two tracers. The difference between the medians was not statistically significant (p = 0.15 by Wilcoxon rank sum test), which may be due to the small sample size.

3.3. Changes in FLT uptake after chemoRT

Overall, FLT accumulation in primary showed significant decrease after chemoRT both visually and quantitatively. In 4 of the 5 patients who underwent FLT PET after chemoRT, SUV_{max} of FLT declined moderately to markedly. These declines measured 54% (patient A, from SUV_{max} of 6.9 to 3.2), 70% (patient D, from 3.9 to 1.2), 81% (patient B, from 8.7 to 1.7), and 85% (patient E, from 6.0 to 0.9) (Fig. 2). The remaining patient F was assessed to have complete resolution of all tumors on both CT and FLT PET, and therefore SUV_{max} was not measured.

Table 2

Tumor size and scan time point.

Tumor size	Median
MR (n = 5, 83%)	4.06
CT (n = 1, 17%)	6.00
Time between FDG1 and chemoRT start (days)	19 (11–22)
Time between FLT1 and chemoRT start (days)	4 (1–16)
Time between chemoRT end and FLT2 (days)	8 (1–21)
Time between FDG1 and FLT1 (days)	12 (4–19)

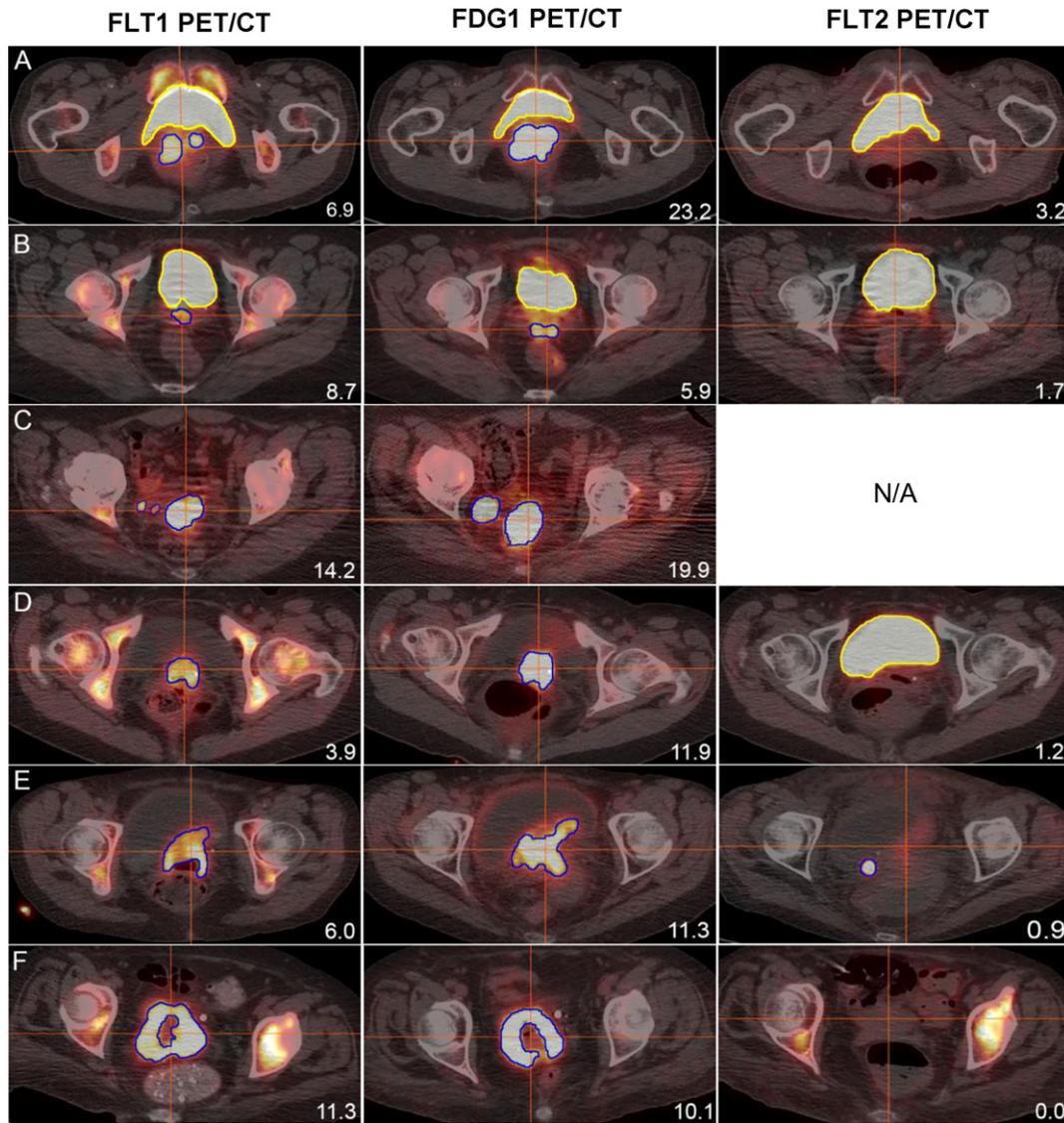


Fig. 1. FLT- and FDG-PET images at diagnosis and post-chemoRT of patients with: stage IIIB vaginal cancer (A) and stages IB2 (B), IIB (C) IIIB (D) and IVA (E and F) cervical cancer. (Patient C did not have post-chemoRT FLT scans.) Blue outlines tumor and yellow traces around the bladder. Values at the lower right corner indicate SUV_{max}.

4. Discussion

In this small pilot evaluation of the role of FLT-PET in imaging gynecologic tumors, we found that FLT uptake in gynecologic cancers before treatment was slightly lower than that of FDG but high enough to be detected and assessed visually and quantitatively. Furthermore, there was a considerable decrease in FLT uptake after chemoRT in all patients who had post-chemoRT scans, suggesting no significant influence of radiation-induced inflammation on FLT uptake.

Greatly increased cell proliferation is a characteristic of many malignant lesions and this cancer-specific process has been exploited in tracer imaging. Retention of FLT, an analog of thymidine, has been shown to correlate with thymidine uptake and thymidine kinase-1 (TK1) activity in cancer cells (Rasey et al., 2002; Toyohara et al., 2002). The fact that only proliferating cells enable thymidine incorporation in DNA synthesis (as opposed to glucose utilization, which is increased in both malignant tissue and inflammatory tissue) makes FLT imaging a particularly attractive tool when differentiating between residual/recurrent malignancy and inflammation.

FLT has previously been shown to be not as significantly affected by post-radiation inflammation and a more specific tracer than FDG when assessing response to radiation therapy, whereas FDG uptake is higher

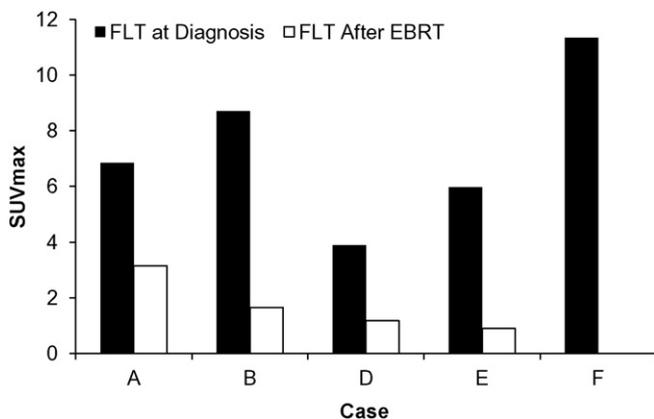


Fig. 2. Changes in SUV_{max} uptake of FLT-PET at diagnosis and postchemoRT. Patient F had complete response. Patient C did not have postchemoRT scans.

than FLT uptake at diagnosis in most tumors (Chen et al., 2015). For example, in laryngeal cancers, FDG uptake was higher than FLT uptake at diagnosis both visually and quantitatively (Been et al., 2009). On the other hand, Kishino et al. found on their mid-treatment scans performed after 40 Gy of radiation therapy that abnormal FLT uptake disappeared in 63% of head-and-neck squamous cell carcinoma lesions whereas FDG uptake disappeared in only 16% of the lesions; specificity was 72% for FLT compared to 19% for FDG. The specificity of FLT-PET (80%) performed after completion of chemoradiation was also higher than that of FDG-PET (48%). However, the sensitivities of mid-treatment and post-RT FLT-PET scans (87.5% and 89%, respectively) were both lower than those of the equivalent FDG-PET scans (100% for both) (Kishino et al., 2012). Van Waarde et al. found similar results in an animal study; using an acute-inflammation model in rats, they demonstrated that FLT is a more cancer-specific PET tracer than FDG, showing no uptake in inflammatory tissues (van Waarde et al., 2004). However, the usefulness of FLT imaging in gynecologic cancers has not been evaluated to date in the setting of post-radiation inflammation. Our results show similar trends when compared to those in other malignancies reported in the literature, such as those for laryngeal and head-and-neck cancer cited above (Been et al., 2009; Kishino et al., 2012; van Waarde et al., 2004).

We would like to acknowledge some limitations of this small pilot study. Although there was a visually significant difference between FLT and FDG uptake by tumors at diagnosis in 4 of 6 patients, the overall difference in SUV did not reach statistical significance, likely due to the small sample size. Also, although our results indicate the feasibility of FLT and its potential usefulness in assessing chemoRT response in gynecologic cancer, exact sensitivity and specificity of post-RT FLT-PET/CT will need to be evaluated in future studies. Furthermore, larger samples are needed to confirm the validity of our findings and to determine the diagnostic accuracy of FLT in this patient population, with the goal of developing quantitative imaging tools that will provide feasible method for triaging treatment and a reliable measurement of the changes after radiation therapy.

5. Conclusion

Overall, FLT uptake in gynecologic cancers was lower than that of FDG at initial diagnosis but was high enough to be detected visually and to be quantifiable in all patients. FLT uptake markedly decreased after chemoRT. These results likely indicate no significant effect of inflammation on FLT uptake. FLT may be a useful tool when assessing the effects of chemoRT on gynecologic cancers and for optimizing post-chemoRT brachytherapy planning.

Disclosure

No potential conflict of interest relevant to this article is reported.

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